REMARKS

Status of Claims

Claims 1-31, 34, 38, 39 and 46 were cancelled previously.

Claims 47-53, and 55-57 are withdrawn.

Claims 32, 33, 35-37, 40-45 and 47-65 are pending and are rejected. More specifically:

Applicants note:

- all claims are rejected under §112;
- claims 60 and 63-65, directed to methods of treatment, are rejected as anticipated;
- claims 40-45 and 58-65, also directed to methods of treatment, are rejected as obvious
- thus, claims 32, 33, 35-37, and 47-57, directed to methods for prevention, are only rejected under §112, and should be allowed upon overcoming the formalities rejections.

The Examiner's attention to this Application is greatly appreciated.

Claim Rejections - 35 USC § 112

Claims 32-33, 35-37 and 54 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement.

The instant claims are drawn to the method for maintaining a healthy bone structure by administration of [1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates] to a patient without an osteopathy.

According to the Examiner, the instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 (undue experimentation); Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 (eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of

working examples; and (8) the quantity of experimentation necessary.

Applicants respectfully traverse in view of the amendment of claim 32.

That is, Applicants agree that the term "osteopathy" is a very broad term, encompassing nerve and muscle as well as skeletal conditions. Claim 32 was intended to claim a method for maintaining a healthy bone structure in a patient not previously diagnosed as being afflicted with a clinically pathologic bone condition. Logically, such a diagnosis would obviously be followed by treatment, not prevention or "maintaining a healthy bone structure". Claim 32 is not intended to claim a method for treatment. To more precisely tailor the claim to the invention, Applicants amend claim 32 based on paragraph [0009] of the specification to a method for maintaining a healthy bone structure, said method comprising administering to a patient without a clinically pathological bone condition a medicament comprising a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates.

Next, Applicants agree that the person of ordinary skill in this art would be a M.D., a Ph.D or at least a M.S. Such a person, having the present specification before him, would easily understand the mechanism of action of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid underlying in the present invention, and would be able to follow the guidance to prescribe a regimen for maintaining a healthy bone structure.

As disclosed in paragraphs [0057] - [0058] of the published specification, it is one of the surprising advantages of the present invention that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid acts to ***avoid the formation of "unfit" bone structures and aids in removing them once they have been formed*** due to its ***selective modulating capabilities*** with respect to the osteoblasts. Therefore, unfit mineralized structures in the bone are prevented and removed respectively. For example, these structures can arise in older people, but have not manifested themselves in clinically pathological conditions yet. Another important example where these unfit structures may occur is the growing skeleton, i.e. children. The present invention provides means for removing these unfit structures or preventing them in the first place, thus contributing to a healthy bone structure which is capable of withstanding the

mechanical stress exerted upon the bone through daily usage.

Given the guidance in the specification, it is easily within the skill of the practitioner to select an appropriate dosage and regimen depending upon desired results, the age, the health, and the physical condition of the patient.

As disclosed for example in paragraph [0054], a particular patient might first require a high degree of inhibition of bone resorption, continue then with low or none and then change again afterwards, according to ***individual requirements which can be determined by biochemical, densitometrical, X-ray or other measurements performed on the bones of the individual.*** (This steering is explained, e.g., at paragraph [0007] "Although it appears that the nature of the R_2 moiety of bisphosphonates determines their anti-resorptive activity, replacement of the hydroxyl group in R_1 by an NH_2 group in some bisphosphonates (e.g. olpadronate and pamidronate) markedly reduces their anti-resorptive activity." And at paragraph [0053] "... So a patient may need a 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid-comprising medicament for bone formation due to the selective modulating effect of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid on the osteoblasts, and at the same time another amino-substituted bisphosphonate for a "tunable" degree of inhibition of bone resorption, depending on his/her individual requirement.)

As disclosed in paragraph [0034], for the selective modulation of osteoblasts and/or for the maintenance of a healthy bone structure and/or for the prevention of osteopathies in healthy patients, etc., administer 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid or any of its soluble salts or any of its hydrates in ***doses of 0.1 to 1000 mg/oral application or 0.02 to 200 mg/parenteral application***.

As disclosed in paragraphs [0046] - [0047], it is preferred that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid be used ***in doses of 12.5 to 75 mg/oral application*** (solid or soluble liquid pharmaceutical formulations, gels, soft capsules, tablets, capsules containing solid preparations, soluble liquid forms or suspensions, and pills),or for topical administration to be applied on skin and/or mucosae, or in ***doses of preferably 2.5 to 15 mg/patenteral application***.

After the application of the medicament in a patient, it is preferably present at extracellular concentrations in a range between 10^{-6}M and 10^{-10}M, more preferably 10^{-7}M and 10^{-9}M, most preferably at an extracellular concentration of about 10^{-8}M.

Accordingly, the specification provides very clear guidance on dosing for maintaining healthy bone structure.

Next, the Examiner comments that the claims herein are directed to treatment of a "patient without an osteopathy". This recitation is interpreted as a patient without any osteopathies. The existing methodology cannot identify with certainty patients that are at risk for osteoporosis.

In response, Applicants refer the Examiner to paragraph [0008] of the specification teaching "In human beings, as of the age of 30, the catabolic processes prevail such that there will be a net loss in total bone substance naturally. Consequently, the rate at which the renewal of the bone tissue takes place will be lowered with increasing age." As taught in paragraph [0039], especially with older people the bones are weakened because of their reduced rate of renewal. As older people may get weaker, the affected bones, in fact, comprise "unfit" mineralized structures and therefore become brittle and unstable which very often is accompanied by a tendency for fractures. These "unfit" structures have not manifested themselves yet as clinically pathological conditions but are less than ideal. They can also be found--apart from in people at or above the age of 40 years--in people recently treated with corticosteroids or in people recently treated with anti-osteoporotic agents such as fluorine and common bisphosphonates such as etidronate and chlodronate. Accordingly, the specification provides guidance as to candidates for a method for maintaining a healthy bone structure, said method comprising administering to a patient without a clinically pathological bone condition a medicament comprising a bone health promoting effective amount of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid, any of its soluble salts or any of its hydrates.

The Examiner comments that osteopathy is a much broader term than osteoporosis. Applicants agree and have amended claim 32 for clarity.

The Examiner takes the position that it is highly unlikely that any of the administration of healthy bone structure can be achieved by the administration of the compositions of the instant application.

In response, Applicants submit that the Examiner is here raising a lack of utility rejection. Applicants submit that pursuant to MPEP 2107.03, evidence of pharmacological or other biological activity of a compound in the specification will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use. *Nelson v. Bowler*, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980).

Further, if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using in vitro assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process.

Accordingly, withdrawal of this grounds of rejection is respectfully requested.

Next, the Examiner points out that the specification does not provide any examples of the administration of NH2-OPD to any patients.

In response, Applicants point out that clinical trials to prove the prophylactic benefits according to the present invention will take decades to complete. It is not possible to withhold filing of a patent application for decades. The only way that evidence could be submitted together with a patent application is, as was done in the present case, by providing in vitro experimentation showing cellular responses known to correlate with in vivo mechanisms. Thus, Applicants have submitted the best possible experimental verification of the invention.

The Examiner indicates that the specification does not provide any guidance for identifying a patient without any osteopathy.

Applicants will concede that the Examiner is correct. Applicants amend "osteopathy" to clinically pathological bone condition.

The Examiner takes the position that lack of working examples is a critical and crucial factor to be considered, especially in cases involving an unpredicatable and undeveloped art. See MPEP § 2164.

In response, Applicants refer the Examiner to MPEP 2107.03, discussed above, and the amendment of the claim to amend "osteopathy" to clinically pathological bone condition.

Response to Arguments

Applicant's arguments filed 1/2/08 have been fully considered but they are not persuasive. Applicants submission of exhibits were fully considered and found unpersuasive since they are directed to detecting osteoporosis rather than ruling out all osteopathies to identify "a patient without an osteopathy". Applicant seems to interchangeably use the terms osteoporosis and osteopathy, not clearly delineating the scope of these two terms.

Applicants agree, and amend "osteopathy" to "clinically pathological bone condition" in claim 32.

Claim Rejections - 35 USC § 112

Claims 32-33, 35-37, 54, and 58-59 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants recite, "said method comprising administering to a patient without an osteopathy." There are no clear cut limitations on when a patient has an osteopathy versus when the patient doesn't. And in the **Response to Arguments** section the Examiner points out "the exhibits are directed to diagnosing osteoporosis, not diagnosing 'a patient with an osteopathy'". Applicants' seem to equate osteoporosis with

osteopathy. These two terms vary in scope and osteoporosis is a subset of osteopathy. Since the claims herein are directed to a patient without an osteopathy, one of skill in the art would need to diagnose all osteopathies, not just a subset of it. The rejection under section 112, second paragraph is deemed proper and is adhered to.

In response, Applicants agree, and submit that amendment of "osteopathy" to "clinically pathological bone condition" in claim 32 removes this grounds of rejection.

Next, Claim 41 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claims recite the phrase, "posttreatment of osteopathies". It is not clear whether the claim require a patient to be free of osteopathies as a result of treatment of osteopathies or whether after some treatment for osteopathies is given. As such, one of skill in the art would not be able ascertain the metes and bounds of the claim herein.

In response, Applicants believe this grounds of rejection is overcome by amendment of "osteopathies" to "a clinically pathological bone condition".

Claim Rejections - 35 USC § 102

Claims 60 (treatment of bone disorder with combination of ingredients) and 63-65 are rejected under 35 U.S.C. §102(b) as being anticipated by Van Beek et. al. (WO 97/02827; of record).

Van Beek et. al. disclose the use of 1-amino-3-(N,N-dimethylamino)- propylidene-1,1-bisphosphonic acid for the treatment of all forms of osteoporosis, arthritis and periodontal diseases, as well as diagnostic purposes. (Page 3, last paragraph to Page 4, line 2; Page 5, Paragraph 3). Beek et. al. further discloses that 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid is devoid of any antiresorptive activity. (page 5, Paragraph 3, lines 1-5). 1-amino-3-(N,N-dimethylamino)-proylidene-1, 1-bisphosphonic acid is disclosed as useful in the treatment of diseases in which antresorptive action is unwanted. . (Page 5, Paragraph 3, lines 5-10). Osteoporosis, arthritis and periodontal diseases are considered bone disorders.

Applicants respectfully traverse.

Van Beek et. al. disclose that 1-amino-3-(N,N-dimethylamino)- propylidene-1,1-bisphosphonic acid is devoid of antiresorptive activity, so that it can be used for

(1) diagnosis, prophylaxis or treatment of urolithiasis. Applicants point out that treatment of kidney stones (calcifications, calculi) requires that the stones be dissolved. This would conflict with an antiresorptive. Thus, Van Beek et. al. teach the benefits of using a compound devoid of antiresorptive activity in the treatment of kidney stones. However, this teaching is limited to kidney stones, which is not a bone disorder. Van Beek et. here do not teach treatment of bone disorder, thus Van Beek et. al. do not anticipate;

(2) ectopic calcifications – again, inappropriate biomineralization occurring in soft tissues, not a bone disorder, thus Van Beek et. al. do not anticipate; and

(3) carriers for other bone active molecules (which is different from treatment of bone disorder, thus Van Beek et. al. do not anticipate.

The Examiner next points out that Beek et. al. discloses the use of said compound in combination with calcium salt, vitamin D and parathyroid hormone. (Page 4, Paragraph 2; Claims 5-10, Page 15). Example 4 and Figure 1 shows binding of bone mineral by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1- bisphosphonic acid as well as olpadronate at various concentrations. Example 5 and Figure 2 shows inhibition of calcium incorporation by 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid and similar compounds.

Applicant maintains the previously submitted argument that Van Beek merely teaches the utility of NH_2-olpadronate in treatments involving kidney stones and biomineralized soft tissue,, and as a carrier for the treatment of various diseases, and not as the active ingredient for treatment of bone disorder. Thus, Van Beek et. al. do not anticipate

Claim Rejections - 35 USC § 103

Claims 40-45 and 58-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Beck et. Al. (WO97/03938; Of record) in view of Brumsen et.al. (Reviews in Molecular Medicine, 76(4), 1997, pp266-283; Of Redord).

Van Beek et. al. is cited for disclosing the use of 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid for the treatment of all forms of osteoporosis, arthritis and periodontal diseases, as well as diagnostic purposes. (Page 3, last paragraph to Page 4, line 2; Page 5, Paragraph 3).

In response, Applicants point out Van Beek merely teaches the utility of NH_2-olpadronate in treatments involving kidney stones and biomineralized soft tissue, and as a carrier for the treatment of various diseases, and not as the active ingredient for treatment of bone disorder. Thus, Van Beek et. al. do not suggest a method for treatment of a patient who has undergone treatment with corticosteroids (claim 40), a method for post-treatment of a clinically pathological bone condition (claim 41), combating bone disease in a child (claim 42), or the "cocktail" of claim 60.

According to the Examiner, Beek et. al. discloses the use of said compound in combination with calcium salt, vitamin D and parathyroid hormone.

In response, Applicants maintain the previously submitted argument that Van Beek merely teaches the utility of NH_2-olpadronate in treatments involving kidney stones and biomineralized soft tissue, and as a carrier for the treatment of various diseases, and not as the active ingredient for treatment of bone disorder.

The Examiner next indicates that Beek et. al. does not expressly disclose the use of NH2-OPD for administration to healthy patients or patients without osteopathies to human being at or above the age of 40 years or to a child or for patients who have undergone corticosteroid treatment or for combating bone disease in a child or any particular dosage range.

Brumsen et. al. discloses the use of 1-hydroxy-3-(N,N-dimethylamino)- propylidene-1,1-bisophosphonate (olpadronate), a molecule with strong structural similarity to 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid. Note that the only difference between the two compounds is the substitution of the hydroxyl group for the amine group at 1-position. Brumsen et. al discloses that long term olpadronate administration to children severe osteoporosis was devoid of any adverse effect on the growing skeleton. (Web printout; Page 20, Paragraph 2). Brumsen et. al. discloses the use of bisphosphonates for patients who underwent

glucocorticoid treatment. (Web printout; Page 21, Paragraph 1). Brumsen et. al further discloses that bisphosphonates are well known for treatment for patients with postmenopausal osteoporosis, a condition generally affecting those above 40 years age. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use 1-amino-3-(N,N-dimethylamino)-propylidene-1,1- bisphosphonic acid to treat children in place of olpadronate because Brumsen et. al. discloses olpadronate for the treatment of children and Beek et. al. discloses 1-amino-3-(N,N-dimethylamino)-propylidene-1,1-bisphosphonic acid to have superior antiresoprtive activity (i.e. lacking the undesired antiresorptive activity) in direct comparison with olpadronate.

Applicants respectfully traverse.

Brumsen teaches that a different bisphosphonate than claimed (olpadronate) is useful for treating osteopathies as a result of its antiresorptive properties. Brumsen teaches against the use of compounds lacking a critical antiresorptive activity. Van Beek teaches that NH_2-olpadronate is useful as a result of its complete lack of antiresorptive properties. One would not read Brumsen to suggest that a structurally related compound that lacks antiresorptive properties (taught by Brumsen to be critical) would be useful for the same purposes as the highly antiresorptive compound olpadronate.

The Examiner's justification for combining the references in that one of ordinary skill in the art would have reasonably expected that the use of [NH_2-olpadronate] as claimed herein would be successful because Beek et. al. showed in comparison with olpadronate, the compound of the instant application has similar or better effects.

Applicant respectfully points out that Van Beek's results do not necessarily indicate that NH_2-olpadronate has "better effects" than does olpadronate.

Van Beek teaches that NH_2-olpadronate binds to bone mineral in a similar fashion to olpadronate (Fig. 1 of Van Beek); that NH_2-olpadronate inhibits calcium incorporation into bone devoid of osteoclast cells in a similar fashion to olpadronate (Fig. 2 of Van Beek); that NH_2-olpadronate inhibits the growth of calcium oxalate monohydrate crystals in a similar fashion to olpadronate (Example 6 of Van Beek); and that NH_2-olpadronate has much less antiresorptive

activity than does olpadronate. Binding to bone mineral and inhibition of calcium absorption into bone are not properties which themselves indicate a compound is useful in treating osteopathy. It was not until the discoveries described in the instant application that NH_2-OPD has a positive effect on osteocalcin synthesis and cytosolic calcium concentrations that the potential for NH_2-OPD to treat and prevent osteopathy became clear. Applicant emphasizes that previously antiresorptive activity was considered a desirable property in the treatment of bone disease; most notably, antiresorptive compounds have been used with success in treating and preventing osteoporosis.

Because Van Beek observed NH_2-olpadronate to bind to bone and bone mineral, but lack antiresorptive activity, Van Beek concluded that NH_2-olpadronate would be a useful carrier for antiresorptive compounds. The carrier will migrate to the bones with the active ingredient, yet not increase antiresorption beyond the level achieved by the active ingredient. The absence of antiresorptive activity alone is no indication that osteopathy can be treated or prevented with NH_2-OPD.

Furthermore, Application points out that NH_2-olpadronate differs from olpadronate in that one compound is in the *cis* conformation, and the other in the *trans* conformation. The transformation from *cis* to *trans* is known to potentially completely change the properties molecule. For example, the analgesic opioids have given rise to antitussives with similar structures, but without narcotic effects.

For the reasons stated above, Applicant respectfully requests the Examiner reconsider and withdraw the rejection. It would not have been obvious to use NH_2-OPD as described by Van Beek for the purposes described by Brumsen.

Accordingly, withdrawal of the rejections and early issuance of the Notice of Allowance is respectfully requested.

The Commissioner is hereby authorized to charge any fees which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment, to Deposit Account Number 16-0877.

Should further issues remain prior to allowance, the Examiner is respectfully

requested to contact the undersigned at the indicated telephone number.

Respectfully submitted,

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